and effective use of methadone for narcotic addict treatment, utilizing the IND and NDA control mechanisms and the authority granted under the Comprehensive Drug Abuse Prevention and Control Act of 1970, to assure that the required additional information for assessing the safety and effectiveness of methadone is obtained, to maintain close control over the safe distribution, administration, and dispensing of the drug, and to detail responsibilities for such control. The conditions established in §291.505 constitute a determination of the appropriate methods of professional practice in the medical treatment of the narcotic addiction of various classes of narcotic addicts with respect to the use of methadone, pursuant to section 4 of the Comprehensive Drug Abuse Prevention and Control Act of 1970.

[39 FR 11680, Mar. 29, 1974, as amended at 41 FR 9546, Mar. 5, 1976; 41 FR 28263, July 9, 1976; 42 FR 46710, Sept. 16, 1977]

§310.305 Records and reports concerning adverse drug experiences on marketed prescription drugs for human use without approved new drug applications.

(a) *Scope.* FDA is requiring manufacturers, packers, and distributors of marketed prescription drug products that are not the subject of an approved new drug or abbreviated new drug application to establish and maintain records and make reports to FDA of:

(1) All serious, unexpected adverse drug experiences associated with the use of their drug products;

(2) Any significant increase in the frequency of a serious, expected adverse drug experience; and

(3) Any significant increase in the frequency of therapeutic failure (lack of effect).

These reports will enable FDA to protect the public health by helping to monitor the safety of marketed drug products and to ensure that these drug products are not adulterated or misbranded.

(b) *Definitions.* The following definitions of terms apply to this section:

(1) *FDA* means the Food and Drug Administration.

(2) *Adverse drug experience* means any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: an adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose, whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.

(3) *Unexpected* means an adverse drug experience that is not listed in the current labeling for the drug product and includes an event that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differs from the event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the labeling only listed cerebral vascular accidents.

(4) *Serious* means an adverse drug experience that is fatal or life-threatening, is permanently disabling, requires inpatient hospitalization, or is a congenital anomaly, cancer, or overdose.

(5) *Increased frequency* means an increase in the rate of occurrence of a particular adverse drug experience, e.g., an increased number of reports of a particular adverse drug experience after appropriate adjustment for drug exposure.

(c) *Reporting requirements—15-day ''Alert reports.''* (1)(i) Any person whose name appears on the label of a marketed prescription drug product as its manufacturer, packer, or distributor shall report to FDA each adverse drug experience received or otherwise obtained that is both serious and unexpected as soon as possible but in any case within 15 working days of initial receipt of the information. Each report shall be accompanied by a copy of the current labeling for the drug product.

(ii) A person identified in paragraph (c)(1)(i) of this section is not required to submit a 15-day ''Alert report'' for an adverse drug experience obtained from a postmarketing study (whether

or not conducted under an investigational new drug application) unless the applicant concludes that there is a reasonable possibility that the drug caused the adverse experience.

(2) Each person identified in paragraph (c)(1) of this section shall submit one copy of each report to the Division of Epidemiology and Surveillance (HFD–730), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

(3) Each person identified in paragraph (c)(1) of this section shall promptly investigate all serious, unexpected adverse drug experiences that are the subject of these 15-day Alert reports and shall submit followup reports within 15 working days of receipt of new information or as requested by FDA. If additional information is not obtainable, a followup report may be required that describes briefly the steps taken to seek additional information and the reasons why it could not be obtained.

(4) Each person identified in paragraph (c)(1) of this section shall review periodically (at least once each year) the frequency of reports of adverse drug experiences that are both serious and expected and reports of therapeutic failure (lack of effect), received or otherwise obtained, and report any significant increase in frequency as soon as possible but in any case within 15 working days of determining that a significant increase in frequency exists. Reports of a significant increase in frequency are required to be submitted in narrative form (including the time period on which the increased frequency is based, the method of analysis, and the interpretation of the results), rather than using Form FDA-1639.

(5) In order to avoid unnecessary duplication in the submission of, and followup to, reports required in this section, including reports required by paragraph (c)(4) of this section, a packer's or distributor's obligations may be met by submission of all reports of serious adverse drug experiences to the manufacturer of the drug product. If a packer or distributor elects to submit these adverse drug experience reports to the manufacturer rather than to FDA, it shall submit each report to the manufacturer within 3 working days of its receipt by the packer or distributor, and the manufacturer shall then comply with the requirements of this section even if its name does not appear on the label of the drug product. Under this circumstance, the packer or distributor shall maintain a record of this action which shall include:

(i) A copy of each drug experience report.

(ii) Date the report was received by the packer or distributor.

(iii) Date the report was submitted to the manufacturer.

(iv) Name and address of the manufacturer.

(6) Each report submitted to FDA under this section shall bear prominent identification as to its contents, i.e., ''15-day Alert report'' or ''15-day Alert report—followup.''

(d) *Reporting form.* (1) Except as provided in paragraph (d)(3) of this section, each person identified in paragraph (c)(1) of this section shall submit each report of a serious and unexpected adverse drug experience on a Form FDA-1639 (Adverse Reaction Report).

(2) Each completed Form FDA-1639 should pertain only to an individual patient.

(3) Instead of using Form FDA–1639, a manufacturer, packer, or distributor may use a computer-generated FDA–1639 or other alternative format (e.g., a computer-generated tape or tabular listing) provided that:

(i) The content of the alternative format is equivalent in all elements of information to those specified in Form FDA–1639, and

(ii) The format is agreed to in advance by the Division of Epidemiology and Surveillance (HFD–730).

(4) Single copies of Form FDA–1639 may be obtained from the Division of Epidemiology and Surveillance (HFD–730), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Supplies of Form FDA–1639 may be obtained from the PHS Forms and Publications Distribution Center, 12100 Parklawn Dr., Rockville, MD 20857.

(e) *Patient privacy.* Manufacturers, packers, and distributors should not include in reports under this section the

names and addresses of individual patients; instead, the manufacturer, packer, and distributor should assign a unique code number to each report, preferably not more than eight characters in length. The manufacturer, packer, and distributor should include the name of the reporter from whom the information was received. Names of patients, individual reporters, health care professionals, hospitals, and geographical identifiers in adverse drug experience reports are not releasable to the public under FDA's public information regulations in part 20 of this chapter.

(f) *Recordkeeping.* (1) Each manufacturer, packer, and distributor shall maintain for a period of 10 years records of all adverse drug experiences required under this section to be reported or reviewed periodically for a significant increase in frequency, including raw data and any correspondence relating to the adverse drug experiences, and the records required to be maintained under paragraph (c)(5) of this section.

(2) Manufacturers and packers may retain the records required in paragraph (f)(1) of this section as part of its complaint files maintained under § 211.198 of this chapter.

(3) Manufacturers, packers, and distributors shall permit any authorized FDA employee, at all reasonable times, to have access to and copy and verify the records established and maintained under this section.

(g) *Disclaimer.* A report or information submitted by a manufacturer, packer, or distributor under this section (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the manufacturer, packer, or distributor, or by FDA, that the report or information constitutes an admission that the drug caused or contributed to an adverse effect. The manufacturer, packer, or distributor need not admit, and may deny, that the report or information submitted under this section constitutes an admission that the drug caused or contributed to an adverse effect.

(Collection of information requirements approved by the Office of Management and Budget under control number 0910–0210)

[51 FR 24779, July 3, 1986, as amended at 52 FR 37936, Oct. 13, 1987; 55 FR 11578, Mar. 29, 1990; 57 FR 17980, Apr. 28, 1993]

Subpart E—Requirements for Specific New Drugs or Devices

§ 310.500 Digoxin products for oral use; conditions for marketing.

(a) Studies have shown evidence of clinically significant differences in bioavailability in different batches of certain marketed digoxin products for oral use from single manufacturers as well as in batches of these products produced by different manufacturers. These differences were observed despite the fact that the products met compendial specifications. Other studies have shown that there is a sufficient correlation between bioavailability in vivo and the dissolution rate of digoxin tablets in vitro to make the dissolution test an important addition to the compendial standards. Because of the potential for serious risk to cardiac patients using digoxin products which may vary in bioavailability, the Commissioner of Food and Drugs has determined that immediate action must be taken to assure the uniformity of all digoxin products for oral use. The Commissioner is of the opinion that digoxin products for oral use are new drugs within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act for which approved new drug applications are required. The Commissioner has determined that, because of questions raised regarding the bioavailability of digoxin products for oral use, there is sufficient evidence to invoke the authority under section 505(j) of the act to fully investigate this question and to facilitate a determination of whether there is a ground for withdrawal of approval of the drug product under section 505(e) of the act. Marketing of these products may be continued only under the following conditions: